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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,920	04/20/2004	John C. Reed	066821-0281	6166

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Cathryn Campbell
McDERMOTT, WILL & EMERY
Suite 700
4370 La Jolla Village Drive
San Diego, CA 92122

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/828,920	REED, JOHN C.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-4,7,8,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/20/2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to papers filed August 31, 2006. Applicant's response to the restriction requirement of July 31, 2006 has been entered. No claims were cancelled or amended, and no new claims were added. Currently, claims 1-11 are pending in the application.

Election/Restrictions

Applicant's election of Group IV (claims 5, 6 and 9), with traverse, drawn to a therapeutic composition comprising a NAC modulating agent, and methods of treating a pathology by administering a NAC modulating agent, is acknowledged. Claims 1-4, 7, 8, 10 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The traversal is with respect to the division of claims in Groups I and IV. Applicant acknowledges that the claims of Groups I and IV are patentably distinct, but argues that the search of the claims of either Group will likely reveal art relevant to the examination of the claims of the other Group, as indicated in the classification of Groups I and IV in the same classes. Thus, the search of their respective subject matter would be duplicative and not be an undue burden.

Applicant's arguments have been fully considered, but not found persuasive, because restriction requirements are set forth for reasons of patentability distinction between each independent invention so as to warrant separate search and search burden, as well as examination. There is no reason to expect the searches to be co-extensive because even though they are related in a subject matter, they are patentably distinct, and would require separate search with different search terms and different search strategy in the art. MPEP 808.02[R-3], under the heading: Establishing Burden, states: "Where the related inventions as claimed are shown to be >independent or< distinct under the criteria of MPEP § 806.05(c) - *> § 806.06<, the examiner, in order to establish reasons for insisting upon restriction, must >explain why there would be a serious burden on the examiner if restriction is not required. Thus the examiner must< show by appropriate explanation one of the following:

(C) A different field of search : Where it is necessary to search for one of the**>inventions in a manner that is not likely to result in finding art pertinent to the other invention(s) (e.g., searching different classes /subclasses or electronic resources, or employing different search queries<, a different field of search is shown, even though the two are classified together. The indicated different field of search must in fact be pertinent to the type of subject matter covered by the claims. Patents need not be cited to show different fields of search".

The fact that Groups I and IV are patentably distinct, has been acknowledged by Applicant. Further, while the subject matter of Groups I and IV may be classifiable in at least two separate classes, the separate classification of their respective subclasses shows them to be further distinct. The Examiner maintains that Groups I and IV are patentably distinct because an anti-NAC antibody and a NAC modulating agent (such as a small organic molecule) are materially different in chemical, physical, and functional properties, and likely have different modes of operation. Each invention therefore employs particulars that are distinct and capable of separate use, thus requiring non-coextensive search and examination.

Applicant timely traversed the restriction (election) requirement in the Paper filed August 31, 2006. The restriction requirement is still deemed proper and is therefore made FINAL. Elected claims 5, 6 and 9 are under current examination.

Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

37 CFR § 1.821 (d) states: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. The amino acid sequences recited in the sequence alignments of Figures 1D and 1E, do not include sequence identifiers. No SEQ ID NOS are present in the brief description of Figures 1D and 1E either.

As it is not clear whether the sequences of Figures 1D and 1E are present in the CRF listing, Applicant is required to check both the as filed paper and CRF sequence listings to ensure concordance with the sequences disclosed in the specification. If the aligned sequences are

present in the sequence listing as filed, the instant application may be placed in compliance with 37 CFR 1.821-1.825 by amending the brief description of the drawings in the specification to refer to the primer sequences by appropriate SEQ ID NOS.

Claim Rejections - 35 USC § 112 – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6 and 9 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims embrace a large number of NAC modulating agents that are not proteins or antibodies constituting a claimed genus. The specification fails to disclose any examples of the numerous non-protein agents that may be described as effective in modulating the association of NAC and NAP proteins. The specification does not describe the structure or functional nature of any non-protein agents that may be described as NAC modulating agents. The specification, while disclosing the association of various NAC and NAP proteins, fails to provide any examples for agents that modulate said association, that thus constitute a claimed genus that encompasses agents yet to be discovered.

As the specification fails to disclose any species of NAC modulating agents, the Artisan of skill could not predict that Applicant possessed any species of said agents.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on numerous species of agents yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of NAC modulating agents. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of numerous NAC modulating agents, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - Lack of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 6 and 9 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for a therapeutic composition comprising any NAC modulating agent, or a method of treating a pathology characterized by abnormal cell proliferation or abnormal inflammation by administering an effective amount of said NAC modulating composition, or a method of modulating transcription of any gene *in vitro*, or *in vivo* comprising contacting a cell with an agent that alters the association of NAC and NAP proteins, as claimed.

This rejection is based on several issues, each indicating an absence of an enabling disclosure for identifying a NAC modulating agent (that is not a NAC protein or an anti-NAC antibody) that is able to alter the association of NAC and NAP proteins; an absence of an enabling disclosure for a method of modulating transcription comprising contacting a cell with said agent; an absence of an enabling disclosure for a therapeutic composition comprising said NAC modulating agent; and an absence of an enabling disclosure for a method of treating a pathology characterized by abnormal proliferation or abnormal inflammation comprising administering an effective amount of said agent. The deficiency was identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets

the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Office has analyzed the specification in direct accordance to the factors outlined in *In re Wands*. MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

As a first issue, the instant specification does not provide an enabling disclosure for identifying a NAC modulating agent (that is not a NAC protein or an anti-NAC antibody) that is able to alter the association of NAC and NAP proteins, or alter transcription. The instant claims recite a method for identification of an agent comprising contacting NAC and NAP associated proteins with an agent and detecting the altered association of said NAC and NAP proteins, wherein said altered association identifies an effective agent.

The specification defines NAC as a protein that contains both an NB-ARC domain and a CARD domain; and NAP as a NAC associated protein. The specification states that a screening assay to identify an effective agent can be performed *in vivo* using the two hybrid system or can be performed *in vitro*, stating: "For example the level of transcription of a reporter gene due to the bridging of a DNA-binding domain and trans-activation domain by a NAP and NAC hybrids can be determined in the absence and in the presence of an agent. An effective agent, which alters the association between NAC and another protein, can be identified by a proportionately altered level of transcription of the reporter gene as compared to the control level of transcription in the absence of the agent." However, the instant specification does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because the description fails to provide any examples of an effective agent, or guidance wherein an agent may specifically alter the association of NAC and NAP

proteins *in vitro* or *in vivo*. The specification does not disclose any instances where NAC and NAP altered association or dissociation are involved in the regulation of transcription of any gene. Each of the Examples provided, involve the association of a NAC and NAP protein and assays showing said association. No dissociation of NAC and NAP proteins is described in any of the examples. The prior art is further silent on the description of an agent that is effective in the specific altered association or dissociation of NAC and NAP proteins. With regards to the use of the yeast two hybrid system for *in vivo* screening, the specification exemplifies NAC and NAP association in Figure 3 and paragraph [00181], and concludes that "$CARD_L$ domain of NAC interacts with the CARD domains of caspase-9 and with Apaf-1." However, in describing protein-protein interactions of NAC in transiently transfected 293T cells, the results showed that NAC interacts with Apaf-1 (Figure 5A), but not with caspase-9 (Figure 6B) and paragraph [00187], thus highlighting the unpredictability inherent in the yeast two hybrid system.
A person of skill in the art would therefore have to engage in additional experimentation to define conditions wherein NAC and NAP associations would be altered *in vitro* or *in vivo*, and further employ a screening procedure to identify and characterize an effective agent. Such further experimentation is regarded as undue and unpredictable, in view of the absence of sufficient guidance in either the instant specification or the prior art.

As a second issue, the specification is not enabling for a therapeutic composition comprising any NAC modulating agent, and a method of treating a pathology characterized by abnormal cell proliferation or abnormal inflammation by administering an effective amount of said NAC modulating composition

It is apparent from the disclosure of the instant application that NAC proteins exert numerous pleiotropic effects (including opposite effects) in an organism. For example, the specification states: "In addition to their role in caspase-activation, CARD domains have been implicated in other cellular processes. Some Card-containing proteins, for example, induce activation of the transcription factor NF-κB ...Card domains are found in some proteins that inhibit rather than activate caspases, such as the IAP..." although caspase activation resulting from CARD domain interactions is often involved in inducing apoptosis, other caspases are primarily involved in proteolytic processing and activation of inflammatory cytokines (such as

pro-IL-1α and pro-IL-18)." (paragraph [0028], p. 10). The specification further states: "In a normal cell, a steady level of association of NAP and NAC proteins likely occurs. This steady state level of association of NAP and NAC proteins in a particular cell type can determine the level of apoptosis in that cell type." (paragraph [00165, p. 54). Therefore, it is unclear how a NAC modulating agent (once identified), would be administered in an effective amount to treat a pathology without affecting normal cells in a patient, where said administration would disrupt the normal steady state level of association of NAP and NAC proteins.

As was indicated in the preceding discussion, the instant specification is devoid of any actual data regarding either an effective NAC modulating agent, or instances wherein said agent is used as a therapeutic composition for treating any of the numerous pathologies that are characterized by abnormal cell proliferation (encompassing diverse conditions from psoriasis to cancer) or abnormal inflammation (encompassing diverse conditions from asthma to arthritis). Moreover, a NAC modulating agent that is an antagonist of a specific NAC-NAP association, may have a deleterious effect in a disease state requiring such association. For example, a cancer treatment using an antagonist agent would likely be ineffective and may serve to increase disease severity by decreasing apoptosis. Additionally, the post-filing art of Ferreira et al. (Clin. Cancer Res. 8:2024-2034; 2002) states: "As far as proapoptotic strategies are concerned, toxicity may represent the potential obstacle to successful clinical development. These approaches are not necessarily based on structural differences between normal and cancer cells. Therefore, achieving tumor cell specificity, while minimizing toxicity, will probably be the major challenge in the development of this type of approach. Tumor cell specificity is not the major concern for apoptosis-permissive strategies, which mainly target cancer cell specific alterations. However, the mechanisms by which apoptosis is facilitated are, thus far, mostly unclear, and only a better mechanistic understanding will allow a more effective exploitation of this secondary apoptotic effect during clinical trials. In general, because of mutations/alterations in the apoptotic machinery, solid tumors have often lost the capacity to undergo instantaneous and massive apoptosis" (first column, p. 2030).

As the prior art is silent on a therapeutic composition characterized as an effective NAC modulating agent, that is further capable of treating diverse pathologies ranging from cancer to arthritis, the person of skill in the art would have to perform a large amount of experimentation

to identify such a therapeutic composition and further test said composition for efficacy in the diverse disease conditions. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. At the time of the instant invention, the skilled artisan not have been able to predict without undue experimentation which agents would qualify as an effective therapeutic.

Therefore, in view of the lack of guidance provided by the specification for the identification of an effective NAC modulating agent and its subsequent use in modulating transcription or treating a pathology characterized by abnormal cell proliferation or abnormal inflammation, it would have required undue experimentation for one of skill in the art to practice applicant's invention as claimed. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is unclear. The claim is directed to a method of modulating transcription. It is unclear whether the method is directed to modulating transcription of a reporter gene, or a heterologous gene, or a chromosomal gene, etc. Thus, the metes and bounds of said "transcription" remain undefined.

Conclusion

Claims 5, 6, and 9 are free of prior art, because elected claims are directed to a NAC modulating agent that is neither a NAC protein nor an anti-NAC antibody. As such, the NAC modulating agent is a non-protein composition.

Claims 5, 6 and 9 are not allowable.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER